REMARKS

This responds to the Final Office Action mailed on March 20, 2009.

Claims 153-154 and 174-175 are amended, claims 169-173 and 177-180 are canceled, and claims 183-184 are added; claims 153-154, 157-165, 174-176, and 181-184 are pending in this application.

The Non-Statutory Obviousness-TypeDouble Patenting Rejection

Claims 153-154, 157-165, 169-175, and 181-182 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 173-194, 196-203, 205-211 and 231 of copending application Serial No. 09/754,775. As neither the present application nor the '775application has been allowed, no terminal disclaimer is required at this time. Should a terminal disclaimer be required, the Office may request it upon a notice of allowable subject matter in either the present application or the '775 application.

The 35 U.S.C. § 112 Rejection

Claims 153-154, 157-165 and 169-182 were rejected under 35 U.S.C. § 112, first paragraph, as lacking adequate enablement. This rejection is respectfully traversed.

In particular, the Examiner asserts that the specification does not teach the administration of any of the claimed compounds in treating a cardiovascular indication in a mammal which indication is characterized by a decreased lumen diameter and so fails to provide information to one of ordinary skill in the art that would allow the practice of the invention without undue experimentation. The Examiner also asserts that it is not predictable from the prior art that all known and yet to be discovered compounds of the recited classes will be useful in the claimed methods and it would require undue experimentation to envision the formulation, dosage, duration, route and appropriate animal model to test the composition

The Examiner is requested to consider that the claims recite either "selecting," "determining" or "identifying" a TGF-beta selevating agent from the recited classes of agents. Given Applicant's disclosure of classes of agents for use in the claimed methods and methods to identify or determine whether a particular agent elevates TGF-beta, as well as cardiovascular

indications characterized by a decreased lumen diameter for which those agents may be efficacious, and the high level of skill in the relevant art, Applicant has enabled the claimed methods.

Moreover, it is Applicant's position that it is within the skill of the art worker in the relevant art to determine the amount of agent and route of administration, as well as an appropriate animal model to test agents. In re Johnson, 282 F.2d 370, 127 U.S.P.Q. 216 (C.C.P.A. 1960) (the selection of suitable dosages is within the skill of the art). See, e.g., Black et al. (U.S. Patent No. 5,464,845), a reference cited against the claims under 35 U.S.C. § 102(e), which discloses administering raloxifene to rats in order to lower serum cholesterol, and the animal models in Examples 4 and 7 of the specification.

Accordingly, withdrawal of the § 112, first paragraph, enablement rejection is respectfully requested.

The 35 U.S.C. § 102 Rejections

Claims 153-154, 157-158, 160-163, 165, 169-173, and 181-182 were rejected under 35 U.S.C. § 102(e) as being anticipated by Black et al. (U.S. Patent No. 5,464,845). Claims 153-154, 157-158, 160-163, 165, 169-173, and 181-182 were rejected under 35 U.S.C. § 102(e) as being anticipated by Fontana (U.S. Patent No. 5,426,123), claims 153-154, 157-158, 160-163, 165, 169-177, and 181-182 were rejected under 35 U.S.C. § 102(e) as being anticipated by Sall (U.S. Patent No. 5,441,965), and claims 153-154, 157-158, 160-163, 165, 169-176, 178, and 181-182 were rejected under 35 U.S.C. § 102(a) as being anticipated by Fontana (U.S. Patent No. 5,384,332). These rejections, as they may be maintained with respect to the pending claims, are respectfully requested.

The present application claims the benefit of the filing date of U.S. application 08/061,714, filed May 13, 1993. The '714 application discloses the use of TGF-beta elevating agents, such as tamoxifen and derivatives and analogs thereof, to prevent or inhibit vascular trauma following an invasive surgical procedure, e.g., restenosis following angioplasty, atheroectomy, placement of a stent, thrombectomy, and vascular rejection following graft or transplant, e.g., vein grafts or transplants or organ allografts, as well as to prevent or inhibit atherosclerosis, coronary heart disease, thrombosis, myocardial infarction, or stroke, indications

or conditions associated with abnormal or inappropriate smooth muscle cell proliferation (pages 3-5 and 17-18 in the '714 application). The active agents include those that inhibit smooth muscle cell proliferation or reduce, delay or eliminate atherosclerotic plaque (page 6 in the '714 application). It is also disclosed that chronically maintaining an elevated level of activated TGF-beta reduces the probability of atherosclerotic lesions (page 14 in the '714 application). It is further disclosed that anti-proliferative amounts may be administered and that the amounts administered are lower than that of tamoxifen to treat breast cancer (pages 15 and 17 in the'714 application).

Therefore, the disclosures in the '123 Fontana patent (which has an effective filing date of May 11, 1994), the Sall patent (which has an effective filing date of December 21, 1993) and the '332 Fontana patent (which has an effective filing date of May 11, 1994) related to the use of tamoxifen analogs to lower serum cholesterol, to inhibit thrombin or to inhibit aortal smooth muscle cell proliferation, are not prior art to claims in the present application entitled to the benefit of the filing date of the '714 application, e.g., claims 153-154 and 174-175.

Moreover, the 123 Fontana patent, the Sall patent and the '332 Fontana patent do not disclose the selection or identification of TGF-beta elevating agents and their use in a mammal with decreased lumen diameter as a result of atherosclerosis, stroke, myocardial infarction or thrombosis, or a mammal having a cardiovascular indication characterized by a decreased lumen diameter and subjected to procedural vascular trauma due to organ transplantation, vascular surgery, transcatheter vascular therapy, vascular grafting, placement of a shunt or placement of an intravascular stent (claims 181-184).

The Black et al. patent has an effective filing date of December 22, 1992. The Black et al. patent discloses the use of raloxifene and structurally related compounds to lower serum cholesterol.

The Examiner is requested to consider the Rule 132 Declaration enclosed herewith, executed by Dr. David Grainger, one of the co-inventors of the present application. In that Declaration, Dr. Grainger states that prior to the effective filing date of the present application, i.e., May 13, 1993, compounds that were considered to be analogs of tamoxifen were also considered to be anti-estrogens. For instance, prior to the effective filing date of the present application, compounds with structural relatedness to tamoxifen were believed to elicit a

beneficial effect as a result of their anti-estrogenic activity. As such, it was understood that the target for those compounds was the estrogen receptor. With regard to the disclosure of the use of raxolifene in Black et al., Dr. Grainger points out that although raloxifene may have some structural relationship to tamoxifen, it does not elevate TGF-beta1 levels.

Therefore, Black et al. do not disclose agents for TGF-beta elevation.

Accordingly, withdrawal of the § 102 rejections is respectfully requested.

The 35 U.S.C. § 103 Rejections

Claim 159 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Black et al., the '123 Fontana patent, the '332 Fontana patent or the Sall patent. Claim 164 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Black et al. in view of Cullinan et al. (U.S. Patent No. 5,457,113, having an effective filing date of October 15, 1993), the '123 Fontana patent in view of Cullinan et al., the '332 Fontana patent in view of Cullinan et al., or over Sall (U.S. Patent No. 5,441,975, having an effective filing date December 21, 1993). These rejections, as they may be maintained with respect to the pending claims, are respectfully traversed.

Applicant need demonstrate only so much of the claimed invention as taught by a cited reference, or what is rendered obvious in view of the reference. In re Stempel, 113 U.S. P.Q. 77 (C.C.P.A. 1957). As discussed above, the '714 application discloses the use of TGF-beta elevating agents, such as tamoxifen and derivatives and analogs thereof, to prevent or inhibit procedural vascular trauma or prevent or inhibit diseases including atherosclerosis, coronary heart disease, thrombosis, myocardial infarction, or stroke. None of Black et al., the '123 Fontana patent, the '332 Fontana patent, the Sall patents nor Cullinen et al. (which disclose the use of raloxifene to inhibit vascular smooth muscle cell proliferation or for restenosis) disclose or suggest the use of TGF-beta elevating agents to prevent or inhibit procedural vascular trauma or prevent or inhibit diseases including atherosclerosis, coronary heart disease, thrombosis, myocardial infarction, or stroke.

Claims 179-180 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Fontana (U.S. Patent No. 5,384,332) in view of Willson (U.S. Patent No. 5,681,835). Claims 179-180 were rejected also under 35 U.S.C. § 103(a) as being unpatentable over Sall (U.S. Patent

No. 5,441,975) in view of Willson. The cancellation of claims 179-180 renders these rejections moot.

Therefore, withdrawal of the § 103(a) rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's representative at (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or deficiencies, or credit any overpayments to Deposit Account No. 19-0743.

Respectfully submitted,

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Date August 12, 2009 By _____
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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being filed using the USPTO's electronic filing system EFS-Web, and is addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on this 12th day of June, 2009.

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